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REVIEW ARTICLE

Patients with left bundle branch block pattern and high cardiac risk myocardial SPECT: does the current management suffice?

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Abstract
Introduction Myocardial perfusion SPECT (MPS) is frequently used for cardiovascular risk stratification. The significance of MPS in patients with abnormal electrical ventricular activation is often questionable. This review assesses the value of MPS for risk stratification of patients with intrinsic left bundle branch block or that due to right ventricular apical pacing.
Methods We reviewed the literature by a search of the MEDLINE database (January 1980 to September 2010). The terms prognosis or prognostic value were combined with SPECT and LBBB or pacing or pacemakers. MPS was categorised as low and high risk according to the original definitions.
Results We identified 11 studies suitable for review. A low-risk MPS is associated with a low risk of cardiac events whereas high-risk MPS carries a 4.8-fold increased risk, 95% CI [3.2 – 7.2] ($p<0.0001$). Despite secondary prevention and an improved medical and interventional care, these figures have hardly changed over time.
Conclusion and clinical implications A low-risk MPS permits a policy of watchful waiting whereas a high-risk MPS requires further analysis and treatment. The persistent high cardiac death and acute myocardial infarction rate after a high-risk MPS suggest that the current management of these patients does not suffice and needs reconsideration.

Keywords Prognosis · LBBB · Pacing · SPECT

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Introduction

Myocardial perfusion single photon emission computed tomography (SPECT) is a well-accepted method for the diagnosis of coronary artery disease [1–4] and for the prognostication of patients [5–7]. However, in patients with an intrinsic left bundle branch block (LBBB) and in patients with right ventricular apical (RVA) pacing, its diagnostic accuracy and prognostic value is reduced [8–12]. False-positive perfusion defects in the septal region in intrinsic LBBB and in the inferoseptal wall in RVA pacing are the main causes of decreased diagnostic accuracy [10–12].

The work-up of chest pain in patients with these specific ECG patterns is cumbersome because all non-invasive techniques fall short in diagnostic accuracy [13]. It is impossible to rule out ischaemia on the exercise ECG due to the inherently abnormal repolarisation [14]. Moreover, due to resting wall motion abnormalities the accuracy of dobutamine stress echocardiography is also disputed [15–17]. The same holds true for any other diagnostic test aiming at demonstrating stress-induced wall motion abnormalities.

In several prognostic myocardial perfusion SPECT studies, the clinical consequences of defects probably related to abnormal activation were evaluated. Several authors claimed that these specific defects were small,

located in well-defined regions and were classified as perfusion defects with a low risk for future cardiac events [18–21]. Addition of functional data from gated myocardial SPECT refined prognostic accuracy by enabling easy recognition of abnormal activation-related defects (AARD). Patients with these AARD and otherwise normal perfusion in the remaining myocardium had a similar favourable prognosis to patients with normal MPS [22].

The present review assesses the value of MPS for risk stratification in patients with LBBB or RVA. Moreover, from the results of the review comments are given on the work-up of these patients and advise on possible treatment options to reduce cardiac risk.

Methods

Candidate studies were identified by several search strategies.

1. Search of the MEDLINE database (January 1980 to September 2010). The terms "prognosis" and "prognostic value" were combined with SPECT and LBBB. This strategy was repeated with pacing or pacemakers instead of LBBB.
2. The reference lists of the reports obtained through these searches were screened for additional articles that may have been missed. Only articles written in the English language and with a follow-up of at least 1 year were selected, whereas reviews and abstracts were excluded.

Studies that used MPS for prognostic purposes in (1) patients with intrinsic LBBB, and (2) patients with LBBB due to permanent right ventricular (apical) pacing were selected. The two groups were studied together since both exhibit similar conduction characteristics on the ECG and secondly due to perfusion abnormalities not related to coronary artery disease that trouble SPECT analysis [8, 10, 23]. Only reports that carried information on the number of cardiac events in terms of prognosis were selected, whereas reports on the diagnostic accuracy of SPECT were left out.

From all selected studies, the number and types of events were listed. When annual event rates were reported these figures were also noted. For each study the following baseline characteristics were recorded: Age, gender, stress protocol, and year of publication. These baseline characteristics were then calculated into a mean for each report. MPS results were categorised as low risk and high risk. The definitions used in the original report were used to categorise low- and high-risk MPS groups. During follow-up only cardiac death and acute myocardial infarction (AMI) were recorded. Heart transplant recipients were categorised as cardiac death.

Statistical analysis

A statistical meta-analysis was performed on the combined AMI and death event rates for the high- and low-risk group with the odds ratio as measure of effect. To obtain the average odds ratio, fixed and random effects models were calculated and the I2 statistic was computed as measure of heterogeneity between studies. For the computations the statistical program R was used (www.R-project.org).

Results

A total of 33 reports were identified. Of these 2 were not written in the English language, 19 did not assess the prognosis of patients with LBBB or RVA pacing with SPECT and 1 study could not be retrieved from the journal [24]. This left 11 articles for review that were carried out in patients with known or suspected CAD [19–22, 25–30]. Two studies from the same investigators with possible double counting or overlap of patients, described the prognostic value of MPS in patients with RVA pacing [20, 21]. Two studies were carried out in a mixed population of LBBB and RVA pacing [22, 30], only the study assessing low- and high-risk MPS in this patient population was used for review [30]. The remaining 10 studies are listed in Table 1.

Prognosis of MPS in RV pacing

Two reports with a total of 201 [20, 21] patients and possible overlap were identified that assessed the prognostic value of MPS with permanent RVA pacing. Patients underwent either pharmacological or exercise stress. The mean age in both studies was >65 years. The authors defined a low-risk MPS as normal scans, scans with small to medium reversible or fixed defects, those with normal cardiac size, and those with normal lung uptake and ejection fractions. The risk of cardiac death and non-fatal AMI was three times higher after a high-risk MPS compared with a low-risk MPS. Patients with a low-risk exercise or adenosine stress MPS result were at a 1014% risk of major cardiac events during the total follow-up (Table 1). Patients with a high-risk MPS had a 2830% risk of major cardiac events. The study characteristics and follow-up details are listed in Table 1.

Prognostic value of MPS in LBBB

Several reports studied the prognostic value of MPS in patients with LBBB [18, 19, 26–29, 31]. One report used

Table 1 Study characteristics

Author	Year	Events	Stress	Patients (n)	Mean age (years)	Follow-up (years)	Males (%)	LBBB / Pacing	SPECT result	CD		CD and AMI		CD and AMI free survival (%)		Annual CD rate (%/year)	
									High risk (n, %)	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
Lapeyre	2005	CD, AMI, Revasc.	Ph.	93	74	5.6±2.4	77	Pacing	23, 25%	n.a.	n.a.	10	7	97	63	1.4	6
Lapeyre	2004	CD, AMI, Revasc.	Ex.	108	68	7.1±2.8	66	Pacing	29, 27%	3	8	8	8	93	81	0.3	3.8
Nigam	1998	NCD, CD	Both	96	66	3.4±2.1	55	LBBB	26, 27%	4	8	n.a.	n.a.	90	65	1.8	10
Nallamothu	1997	CD, AMI, Revasc., HTx	Both	293	58	2.8±2.3	59	LBBB	167, 57%	n.a.	n.a.	11	47	91	72	n.a.	n.a.
Gil	1998	CD, AMI, Revasc.	Ph.	69	59	2.8	48	LBBB	n.a.	0	n.a.	0	n.a.	100	n.a.	0	n.a.
Wagdy	1998	CD, AMI, Revasc., NCD, CAG, HTx	Ph.	245	69	3±1.4	51	LBBB	84, 34%	6	20	9	27	93	55	n.a.	n.a.
America	2007	CD, AMI, Revasc.	Ph.	101	65	1.24 (max 2.48)	67	LBBB	101, 100%	n.a.	14	n.a.	15	n.a.	n.a.	n.a.	n.a.
Krishman	1993	CD, Revasc.	Both	69	68	2 (1.5 2.7)	61	LBBB	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Usmani	2009	CD, AMI	Ph.	76	56	24±8 (months)	58	LBBB	24, 32%	1	5	3	8	98	79	1	11
ten Cate	2010	CD, AMI, Revasc.	Ph.	197	69	2.6±1.5	37	Both	96, 49%	2	13	4	17	97	77	0.7	6.4
Total				1347	65	3.2			550, 41%	16	68	45	129				

AMI = acute myocardial infarction, *CAG* = coronary angiography, *CD* = cardiac death, *Ex.* = exercise, *HTx* = heart transplant, *LBBB* = left bundle branch block, *n.a.* = not available, *NCD* = non cardiac death, *Ph.* = pharmacological, *Revasc.* = coronary revascularisation, *SPECT* = single photon emission computed tomography

the exercise characteristics for the prognostic value assessment and did not describe the results of the MPS. This study was subsequently not excluded from this review [31].

A total of 949 patients were evaluated and categorised to low or high risk based on the MPS results. Patients underwent either pharmacological stress or exercise stress. The study and follow-up details are listed in Table 1. The studies were carried out mostly in a relatively old patient population with a mean age of more than 65 years and mixed MPS results. One report describes the results of abnormal MPS [26] and another was restricted to normal MPS results in a relatively young patient population (59 years) [28]. Also, the endpoints differ between the reports. However, the cardiac death rate was <2% after a low-risk MPS compared with up to 15% after a high-risk MPS. The combined endpoint cardiac death and non-fatal AMI was up to 7% for patients with a low-risk MPS compared with 25% for those with a high-risk MPS.

Myocardial perfusion SPECT in a mixed population of LBBB and RVA pacing

A more recent report assessed the prognostic value of MPS in 197 patients with LBBB or RVA pacing [30]. The study characteristics are described in Table 1. Unlike earlier reports [18, 19, 27], wall motion analysis in conjunction with the perfusion results was used to define a low-risk MPS. This allows defining AARD. Patients with only AARD and otherwise normal myocardial perfusion demonstrated a similar prognosis to patients with the same conduction characteristics and normal myocardial perfusion on MPS [22]. Hence, both MPS results were considered to be low risk and compared with all other MPS results that were considered high risk [30]. The annual cardiac death rate was <1%/year in patients with low-risk MPS whereas this figure was >6%/year for high-risk patients. Patients with a high-risk MPS had much higher cardiac death and non-fatal AMI rate of 18% compared with 4% for those considered at a low risk ($p<0.001$) [30]. No difference in prognosis between patients with LBBB or RVA pacing was found.

Meta-analysis

Based on the results derived from the studies that reported the number of cardiac death and non-fatal acute myocardial infarctions (Table 1) a meta-analysis was performed. The average odds ratio over the 6 studies was 4.8 [95% CI, 3.3 – 7.2] ($p<0.0001$) for the fixed effects model and 4.8 [95% CI, 3.3 – 7.1] for the random effects model ($p<0.0001$). The I2 was 0% [95% CI, 0 – 66]. This implies that patients with a high-risk MPS were at a

4.8-fold increased risk of cardiac death or non-fatal AMI as compared with patients with a low-risk MPS.

One institutional management outcome

In view of the above-mentioned outcome and because detailed data about the treatment in the cited reports are missing, we present the St Antonius Hospital results of the management of patients with LBBB pattern and high-risk MPS. The choice of the medical, invasive or combined treatment was left to the discretion of the cardiologist in charge (Table 2). In the high-risk group, medical treatment was the predominant choice of therapy, whereas 44% (n=42) were referred for further invasive assessment and 57% of these patients underwent revascularisation. The majority of patients were on a treatment regime of aspirin, statin treatment and β-blockers (Table 3) ($p<0.001$). Nevertheless, cardiac death and non-fatal AMI still occurred in about 18% of patients and most cardiac deaths could be classified as sudden cardiac death. Only 2 patients died of heart failure, and 1 died of fatal myocardial infarction. However, if coronary revascularisation was performed in these high-risk patients, cardiac death or non-fatal AMI were not observed. When patients underwent coronary angiography but were treated medically one non-fatal AMI was observed. Compared with patients with a low-risk MPS, the patient population with a high-risk MPS had a lower mean LVEF (59% versus 38% respectively). Also a previous myocardial infarction was observed more in the group with a high-risk MPS compared with group with a low-risk MPS.

Discussion

MPS is a well-established method to stratify patients at low or high risk for cardiac events to come. This is especially true when the left ventricular activation pattern is normal [5–7]. The present review demonstrates discrimination between low and high risk, which also holds true in patients with an LBBB pattern. The described annual cardiac death rates for a low-risk MPS varied between 0 and 1.8% in this patient population, whereas a high-risk MPS was associated with an annual cardiac death rate between 3.8 and 10%/year. Especially for patients with a high-risk MPS these figures are higher than expected based on the results of previous studies in patients without an abnormal left ventricular activation pattern.

The definition of low-risk MPS in LBBB or RVA pacing

Several reports defined a low-risk MPS in this patient population in the pre-gated SPECT era as completely normal scans, small to medium reversible or fixed defects, normal ventricular volumes and ejection fractions [18, 20, 21, 27, 28]. Since the introduction of gated SPECT it could be demonstrated that these low-risk MPS in an LBBB and RVA pacing population can be defined on the basis of combined perfusion and wall motion analysis. With the use of gated SPECT abnormal perfusion could be attributed to the abnormal left ventricular activation pattern.

Table 2 Post-SPECT strategy

	CAG			Medical treatment		
				Reason		
	Revascularisation	Medical treatment		Small ischaemic burden	Good response to medical therapy	Risk of CAG or subsequent revascularisation considered too high
		Reason				
		Revascularisation not possible	Coronary artery disease <70%			
SPECT infarct only (N=16)	2 [CABG=1]	1	1	9 [NCD=1, CD=3]	1	2
SPECT infarct and ischaemia (N=52)	15 [PCI=2, CABG=1]	4 [NCD=1]	3 [PCI=2]	13 [NCD=1, CD=1]	11 [CD=6, PCI=1]	6 [CD=2, MI=1]
SPECT ischaemia only (N=28)	7 [CABG=2, PCI=1]	4 [MI=1]	5 [PCI=1]	4 [MI=1]	4 [PCI=1]	3 [CD=1, MI=1]

AARD = abnormal activation related defects, *AMI* = acute myocardial infarction, *CABG* = coronary artery bypass graft, *CAG* = coronary angiography, *NCD* = non-cardiac death, *PCI* = percutaneous coronary intervention, *SPECT* = single photon emission computed tomography

The number and type of events are given between brackets

Table 3 Medical strategy after MPS

	Low-risk (n=101)	High-risk (n=96)
Beta-blocker (n, %)	54 (53%)	86 (90%)
Aspirin (n, %)	66 (65%)	69 (72%)
Warfarin (n, %)	31 (31%)	36 (36%)
Statin (n, %)	58 (57%)	88 (92%)

Patients could be on aspirin, warfarin or aspirin and warfarin therapy

A triad of abnormal left ventricular activation pattern, perfusion abnormalities in well-defined regions and concomitant wall motion abnormalities in the same regions was considered to be only AARD and not related to coronary artery disease [22]. These AARD demonstrated to have a similar prognosis to normal MPS in patients with the same LV conduction characteristics. Therefore, it was concluded that these AARD are strictly related to the specific activation pattern and have no consequences for the prognosis.

The prognostic value of MPS

Perspective on cardiac event rates in patients with LBBB or RVA pacing

Several issues arise when studying the results of the prognostic studies in more detail. First, reports on the prognosis of MPS for patients with either LBBB or RVA pacing are scarce. While several thousands of patients are studied with normal LV activation patterns, only about 1250 patients with abnormal left ventricular activation patterns were previously reported. The majority of these studies were published before 1993 and therefore the reported prognostic value may have changed over time with improved pharmacological and invasive treatment. Furthermore, most studies were carried out without gating [18–21, 27, 28]. Various sorts of events were assessed and the patient population was rather old with a mean age of >65 years and most patients showed a relatively high pre-test probability for coronary artery disease.

A normal- or low-risk MPS demonstrated a lower event rate than a high-risk MPS in these patients (Table 1) [18–21, 27]. It is stressed that these figures are higher compared with low- and high-risk MPS in patients with a normal left ventricular activation [5, 6, 32]. This difference may be explained by several important findings. First, the prognosis of MPS in patients with LBBB or RVA pacing was assessed in patients with a higher mean age compared with studies that assessed the prognostic value of MPS in patients with normal left ventricular conduction. Also, patients with LBBB are known to have a higher cardiac event rate than patients with right bundle branch block or normal left ventricular activation patterns [33–35]. For RVA pacing this is less well known. The presence of ventricular pacing does not seem to influence mortality [36, 37], but atrial fibrillation and heart failure are more often observed with chronic RVA pacing [38, 39].

High-risk MPS in patients with LBBB and RVA pacing

Despite the fact that treatment was instigated based on the MPS results, the presence of an abnormal MPS in these patients carries the risk of a very high cardiac event rate [18, 19, 26, 27]. These figures are significantly higher than those of patients with a low-risk MPS and the same conduction characteristics [18, 19, 22, 27, 28]. This suggests that MPS is capable of identifying patients at low and high risk for future cardiac events, even in the presence of LBBB and RVA pacing. This suggestion is strengthened by the odds ratio of 4.8 between patients with a low- and high-risk MPS, an outcome that hardly differed between the studies used in the meta-analysis.

Clinical implications

Despite improvements in therapeutic care over time in terms of medication, invasive examination and interventions, the observed cardiac death and non-fatal AMI rates hardly differ over time (Table 1). One would assume that the event rates would diminish in more recent reports since patients are treated based on the results of the MPS and the better therapeutic modalities. Our management of this patient category also disclosed unsatisfying results. The reasons for this lack of improved outcome in more recent years remains unclear [19–21, 25–27]. The data suggest that patients with an LBBB or RVA pacing and an abnormal MPS who cannot be treated with coronary revascularisation are especially at a high risk of sudden cardiac death or non-fatal AMI (Table 3: 0 events after revascularisation versus 17 events with medical treatment). Because cardiac death in the medically treated high-risk MPS group was mainly acute and unexpected, one could argue whether treatment should focus on prevention of sudden cardiac death, especially when coronary revascularisation is not feasible or indications for ICD implantation are absent. Whether this approach for this specific patient category would improve the outcome remains a future study target.

Conclusion

In the presence of an abnormal left ventricular activation pattern, MPS remains a powerful technique for risk

stratification. A normal- or low-risk MPS is associated with a relatively uneventful follow-up. Despite treatment based on the MPS results, the cardiac event rate of patients with high-risk MPS is significantly higher than expected from data of patients without LBBB or RVA pacing and therefore requires upgrading of management.

Conflict of interest There are no conflict to declare

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